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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,167	03/07/2005	Joyce A. DeLeo	DC-0301	5784

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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	PAPER NUMBER
1649	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)	
	10/521,167	DELEO, JOYCE A.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claim 1 is pending and under examination in the instant office action.

Information Disclosure Statement

A signed and initialed copy of the IDS paper submitted January 14, 2005 is enclosed in this action.

Specification

The disclosure is objected to because of the following informalities:

At page 9, line 28, the author's name "Abbadle" is spelled incorrectly. The author's name is correctly spelled "Abbadie", as listed on the IDS.

At page 10, lines 1-2, there is an incomplete sentence that begins "It has been suggested that CCR2..." The Examiner cautions Applicant to be conscientious in the correction of this sentence, so as to avoid the introduction new subject matter.

At page 10, line 34, the units for the dose of MCP-1 neutralizing antibody is written as "20 mg", wherein the Examiner assumes the unit dosage is meant to be "20 μg", which would be consistent with the Tables 4 and 5.

At page 17, lines 1-2, the phrase "spinal mRNA *leves was* analyzed [sic]" may represent a typographical error. It is assumed the phrase is meant to recite: "spinal mRNA levels were analyzed".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing pain characterized by an increase in monocyte chemoattractant protein-1 (MCP-1) levels, comprising administering to a mammal having said pain an effective amount of a MCP-1 neutralizing antibody or binding fragment thereof, thereby reducing pain in the mammal, does not reasonably provide enablement for a method of preventing pain or treating any type of pain in a mammal comprising administration of a MCP-1 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The claim is broadly drawn to a method for preventing or treating pain comprising administering to a mammal at risk of having or having pain an effective amount of a monocyte chemoattractant protein-1 (MCP-1) antibody or binding fragment thereof, thereby respectively preventing or treating pain in the mammal. The Examiner notes that the instant claim does not require that the mammal actually have a pain, and thus the instant claims encompass prophylaxis. EVERY mammal is in need of prophylaxis to prevent pain because every mammal is at risk of having pain. Accordingly, the claims broadly encompass administration of a MCP-1 antibody to any mammal at any time.

The nature of the invention is the demonstration that MCP-1 mRNA and protein are elevated following L5 spinal nerve transaction in rodents, which is an art-accepted animal model employed for neuropathic pain research. Applicant demonstrates that intrathecal administration of a high dose (20 μg) of MCP-1 neutralizing antibody was capable of significantly attenuating mechanical allodynia following nerve injury, whereas a lower dose of the MCP-1 antibody (4 μg) was ineffective in reducing mechanical allodynia in nerve-injured rats (Tables 4 and 5). The art defines mechanical allodynia as pain from stimuli which are not normally painful, such as pain from light touch or pressure to the skin in the area of the damaged nerve. The instant application thus teaches that the administration of MCP-1 antibody at a high dose (i.e., an effective amount) can attenuate a particular type of pain, mechanical allodynia, in animals having elevated levels of MCP-1 in their spinal cord tissue due to nerve injury.

Applicant extrapolates these findings to assert that administration of a MCP-1 antibody to a mammal will prevent or treat all types of pain. Applicant demonstrates

and the prior art recognizes that the MCP-1 expression is upregulated following nerve injury (see, for example, Flügel et al. *J. Cerebral Blood Flow Metabol.* 2001; 21:69-76). The recognition that chemokines may enhance the perception of pain through desensitization of opioid receptors is also noted in the prior art (see Szabo et al. *Proc Natl Acad Sci USA*, 2002; 99(16):10276-10281). However, while the level of skill in the art is high, the level of predictability is quite low. The art recognizes that different animal models of pain result in distinct neurochemical signature at the level of the spinal cord and afferent pain signaling pathways. For example, Honore et al. (*Neurosci.* 2000, 98(3):585-598) report that whereas an inflammatory pain model (injection of complete Freund's adjuvant into the hindpaw) lead to increases in spinal substance P, substance P receptors, CGRP, and protein kinase Cγ, a neuropathic pain model (sciatic nerve transection or L5 spinal nerve ligation) demonstrated significant *decreases* in substance P and CGRP and increases in galanin and NPY. In contrast, a model of cancer pain induced by injection of osteolytic sarcoma cells into the femur, produced no detectable changes in any of these markers in either primary afferent neurons or the spinal cord (see abstract). Honore et al. thus conclude that inflammatory, neuropathic and cancer pain models each generate a unique and highly distinct set of neurochemical changes in the spinal cord and dorsal root ganglia, and it is presently undetermined to what extent these changes are involved in the generation and/or maintainence of each type of pain (see p. 595, 2nd column). The prior art is silent with respect to whether or not MCP-1 protein or mRNA levels are increased in pain models other than nerve transection/ligation or in pain models other than neuroinflammation. The instant

specification does not provide sufficient guidance – nor does the prior art teach – whether or not cancer pain, for example, would elevate MCP-1 levels, or whether acute pain, such as touching a hot surface or stubbing a toe, would lead to an increase in MCP-1 levels in the spinal cord. Additionally, Winkelstein et al. (*J. Comp Neurol.* 2001; 439: 127-139) note that even when similar pain models are used, resulting in similar neuroimmune profiles and behavioral responses (mechanical allodynia and thermal hyperalgesia), different treatments may be necessary for effectively alleviating pain in neuropathic versus radicular pain, as evidenced by the fact that pharmacologic treatments that were efficacious in one model were ineffective in the other (see in particular p. 138). Thus, the complex nature of the invention does not allow the skilled artisan to predict the effects of MCP-1 antibody administration for purposes of prevention of pain in a mammal at risk of developing pain, nor does it allow the skilled artisan to predict that the antibody will be efficacious in treating of other types of pain, such as cancer pain or acute pain, which may or may not result in elevation of MCP-1 levels.

Furthermore, "prevention" is understood in the art to encompass total protection from disease or injury – prevention requires 100% efficacy. That is, no mammal treated with the antibody develops pain of any kind at any time. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The instant specification, however, fails to teach that the administration of the particular claimed antibody or binding fragments thereof is/are able to completely prevent pain of any kind in a mammal.

Given the lack of working examples involving prevention or prophylaxis of pain and/or treatment of any kind of pain due to any cause, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to practice the claimed invention, while the claims encompass methods reciting prevention or prophylaxis of pain and/or treatment of pain due to a plurality of causes, the specification only teaches one skilled in the art to use an anti-MCP-1 neutralizing antibody in nerve-injured animals verified to have elevated MCP-1 levels in order to reduce pain associated with mechanical allodynia. Therefore, it would require undue experimentation for one of skill in the art to practice the claimed invention commensurate with the scope of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Ogata et al. (*J. Pathology*, 1997; 182:106-114).

The claim is directed to a method for preventing or treating pain comprising administering to a mammal at risk of or having pain an effective amount of a monocyte chemoattractant protein-1 (MCP-1) antibody or binding fragment thereof. It is noted that the instant claim does not require that the mammal actually have pain, since the instant

claim encompasses prophylaxis. Because every mammal is in need of prophylaxis from pain, any disclosure of administering a MCP-1 antibody to a mammal for any reason is pertinent to the instant claims.

Ogata et al. teach that MCP-1 is involved in the pathogensis of collagen-induced arthritis in rats. Rats immunized with collagen develop arthritis, as assessed by swelling and redness in the hind paws which precedes severe arthritis of the ankle joints, prominent infiltration of neutrophils and macrophages in the inflammatory synovium, and significantly increased levels of MCP-1 in synovial lavage fluids and synovial tissues (see, for example, Figures 2-5). Ogata et al. teach that rats injected with an anti-MCP-1 monoclonal antibody (mAb) had significantly suppressed hind foot swelling compared to arthritic rats treated with an irrelevant isotype-matched control mAb (see Figure 9). Patients suffering from arthritis, particularly severe arthritis, are known to have pain associated with the arthritis. As such, the arthritic rats in these studies would undoubtedly also have pain. Therefore, administration of the anti-MCP-1 mAb to these rats, which was shown to successfully reduce arthritis-induced swelling, would also inherently treat the pain associated with the arthritis. Accordingly, the teachings of Ogata et al. anticipate instant claim 1.

Conclusion

Claim 1 is not allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Kimberly Ballard, Ph.D.
January 12, 2007

ELIZABETH KEMMERER
PRIMARY EXAMINER